REMARKS

I. Declaration

In support of the present Amendment, Applicants submit a Declaration under 37 C.F.R. §1.132 in the name of Anne Mari Juppo (the "Declaration"). An unsigned version of the Declaration is being submitted at this time. The signed, original Declaration will be submitted in due course.

II. The claimed invention

The claimed invention is directed to a method for the preparation of homogeneous microparticles comprising a pharmaceutically active substance and a polymer. The pharmaceutically active substance and the polymer are suspended, dissolved, or emulsified in a solvent. The resultant suspension/solution/emulsion is atomized into droplets and then frozen. The frozen solvent is removed from the frozen droplets by sublimation, yielding dry, homogeneous microparticles.

Advantageously, the homogenous microparticles obtained with the claimed method are characterized by a small pore size, low friability, and a high content of the pharmaceutically active substance (See page 6, lines 16-25) It was unexpectedly discovered that the success in obtaining stronger microparticles, i.e., porous microparticles having low friability, depends on the volume fraction of dry materials and the amount of polymer binder (See page 7, lines 11-14). Therefore, in accordance with the claimed invention, the minimum dry content of the suspension/solution/emulsion from which the droplets are formed is 15% by volume and the polymer binder content is at least 5%.

III. Claim rejection - 35 U.S.C. § 112

Claim 14 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point and distinctly claim the subject matter which Applicant regards as the invention.

It is respectfully submitted that amended claim 14 overcomes the rejection. Support is provided by original claim 1. Accordingly, no new matter has been introduced by the claim amendment.

Withdrawal of the §112 rejection is requested.

IV. Claim rejection – 35 U.S.C. §103

Claims 1-23 are pending. According to the final Office Action, claims 1-20 are rejected under 35 U.S.C. §103(a) as being unpatentable over GB 2,329,124 to Ratwatte ("Ratwatte").

Applicant's arguments of record can be summarized as follows. Applicant has argued that Ratwatte neither discloses nor suggests the recited volume fraction of dry materials and the amount of polymer binder which characterize the claimed invention. Applicant has also argued that these limitations, i.e., a minimum dry content of at least 15% by volume and polymer binder content of at least 5%, are essential to obtain the claimed microparticles and advantageous properties, i.e., small pore size, low friability, and a high content of the pharmaceutically active substance.

The Examiner has not disagreed with Applicant. In the final Office Action, the Examiner states that Applicant has relied on data pertaining only to the claimed invention. To show any patentable distinction, the Examiner stipulates at page 6 of the final Office Action that this data

must be compared to the prior art. According to the Examiner, the comparison should show that a "better result" is achieved based solely on the dry weight and amount of polymer.

A. Ratwatte discloses methods for the preparation of non-homogeneous and homogeneous particles.

Example 1 of Ratwatte discloses a method for the preparation of a coated particle. According to Example 1, an agent composition is dispersed in a solution of a coating material in a liquid carrier material to form a dispersed mixture which is then sprayed to form droplets of the dispersed mixture. The droplets are frozen and dried to produce a plurality of coated individual particles.

The coated particles of Example 1 of Ratwatte are not described as having a uniform composition or structure. Therefore, the coated particles of Example 1 of Ratwatte are not described as being homogenous. This is consistent with the technical definition of the term "homogenous" when used to describe a chemical substance:

> **Homogenous** [CHEM] Pertaining to a substance having uniform composition or structure. McGraw-Hill, *Dictionary of Scientific and Technical Terms*, 2d Edition, 1978.)

Example 2 of Ratwatte appears to disclose a method of preparing homogenous microparticles. However, Example 2 of Ratwatte does not disclose or suggest the claimed method of preparing homogeneous microparticles. (Declaration at ¶7C) In accordance with Example 2 of Ratwatte, a mixture is formed by adding a drug to a stabilizing formulation consisting of water, a carbohydrate and a surfactant. Both the carbohydrate and surfactant are soluble in water. ***In contrast to the claimed invention, polymer is absent from the mixture used by Ratwatte in Example 2.*** The mixture without polymer is sprayed from a nozzle into a moving

stream of air that is cooled below the freezing point of the mixture to form frozen droplets which are freeze-dried to produce particles consisting of a homogenous mixtures of the drug and stabilizing formulation. At page 12, lines 7-10, Ratwatte discloses that the thus prepared particles of Example 2 can be coated in the same way as the drug crystals were coated in Example 1.

Due to the absence of polymer in the mixture used by Ratwatte in Example 2, the homogeneous particles prepared thereby have a structure that is different from the homogenous microparticles prepared in accordance with the claimed invention. (Declaration at ¶7C)

In summary:

- Example 1 of Ratwatte is directed to the formation of coated, non-homogeneous particles. Therefore, Example 1 and the corresponding disclosure of Ratwatte do not suggest the claimed invention directed to homogeneous microparticles and methods for preparing same.
- The particles of Example 2 of Ratwatte are formed from a mixture without polymer. In contrast, the claimed invention requires polymer in an amount at least 5% by weight based upon the dry content of the liquid medium. As such, Example 2 and the corresponding disclosure of Ratwatte do not suggest the claimed method of preparing homogenous microparticles and the microparticles prepared by the claimed method. (Declaration at ¶7C)

B. The Declaration and comparative data shows that a better result is achieved with the claimed invention.

The microparticles prepared in accordance with the claimed method have superior mechanical strength relative to the homogenous pellets disclosed by Ratwatte and prepared in accordance with Example 2. (Declaration at ¶10)

A working example of the claimed invention is provided by Example 1. In Example 2 of the present application, the homogeneous particles of Example 1 were coated by a fluidized bed coating process without disintegrating or otherwise losing their shape and structural integrity. It is an advantage of the claimed invention that the microparticles posses the mechanical strength to retain their shape and structural integrity during a coating process. (Declaration at ¶9)

The Declaration provides another working example of the claimed invention, i.e. Example 3. In addition, the Declaration provides a side-by-side comparison based on the variables "dry weight" and "amount of polymer", as recited in the claims. Only Examples 1 and Example 3 meet the requirements of the claimed invention wherein the minimum dry content of the suspension/solution/emulsion from which the droplets are formed is 15% by volume and the polymer binder content is at least 5%. In Examples 4-10, the minimum dry content and/or polymer binder content deviate from the express requirements of the claimed invention.

As can be seen from Table 2 of the Declaration, the mechanical properties of the microparticles are a function of the relationship between the minimum dry content and the polymer binder content. (Declaration at ¶9)

Table 2. Characterization of microparticles

Example no	Dry content (wt%)	Dry content (vol %)	Binder (wt%)	Mercury porosity measurements		Mechanical strength	
				Bulk density	Pore median size (μm) (measured range: 0.0005-10μm)	kPa	Fraction
1	34	19.2	21	0.47	0.8	94	450-630 μm
3	31.8	17.7	21	0.48	0.7	125	300-400 μm
4	19.4	10	21	0.23	1.8	62	300-400 μm
5	26	12	5	0.35	1.6	25	300-400 μm
6	23	9.8	0	Not measured		Too fragile for handling	
7	12	4.7	0	Not measured		Too fragile for handling	
8	38.5	19.1	0	Not measured		Fragile, not coatable	
9	40	20.3	1.5	Not measured		Fragile, not coatable	
10	40	20.6	3	Not measured		Fragile, not coatable	

The particles of Examples 1 and 3 possess the mechanical properties to be successfully coated by a fluidized bed coating process without disintegrating or otherwise losing their shape and integrity. The particles of Examples 4-10, wherein the minimum dry content is less than 15% by volume and/or the polymer binder content is less than 5%, are either too fragile for handling or do not possess the threshold mechanical properties to be coated by a fluidized bed coating process without disintegrating or otherwise losing their shape and integrity.

Furthermore, as discussed in the preceding Section IVA, Example 2 of Ratwatte and the corresponding disclosure use a mixture ***without polymer*** to prepare microparticles. It is evident from the preceding the Declaration and Table 2 that the particles of Examples 6-8, which were prepared without polymer, i.e., a binder, are too fragile and not suitable for coating. (Declaration at ¶9)

Advantageously, the homogenous microparticles obtained with the claimed method are characterized by a small pore size, low friability, and a high content of the pharmaceutically active substance. It was unexpectedly discovered that the success in obtaining stronger microparticles, i.e., porous microparticles having low friability, depends on the volume fraction of dry materials and the amount of polymer binder. (Declaration at ¶6) In accordance with the claimed invention, the minimum dry content of the suspension/solution/emulsion from which the droplets are formed is 15% by volume and the polymer binder content is at least 5%.

It is clear that Ratwatte fails to appreciate the significance of the respective percentage of the dry content and polymer binder in the preparation of microparticles. Accordingly, at the time the claimed invention was made, Ratwatte would have provided no motivation to persons in the art to apply their skills to seek a method of preparing and improving the mechanical properties of microparticles comprising a pharmaceutically active substance. Therefore, Accordingly, withdrawal of the §103(a) rejection in view of Ratwatte is respectfully requested.

In summary:

- The properties of the microparticles are a function of the relationship between the minimum dry content and the polymer binder content.
- The comparative data demonstrates that an unexpected improvement in mechanical properties is obtained with the claimed invention.
- A better result is obtained when the minimum dry content is less than 15% by volume and/or the polymer binder content is less than 5%. This advantage is not suggested by Ratwatte. (See Example 2 of Ratwatte and Examples 6-8 of the Declaration)

For all of the foregoing reasons, withdrawal of the §103 rejection is requested.

V. Claim rejection - 35 U.S.C. § 102

Claims 18 and 19 are rejected under 35 U.S.C. §102 as being anticipated by Ratwatte. The Examiner correctly identifies claims 18 and 19 as product-by-process claims. Patentability of such claims depends on the product and not on the method of producing the product.

Anticipation requires that each every feature of a claimed invention be disclosed within the four corners of a single reference. Applicant submits that Ratwatte fails to disclose, either expressly or inherently, the features of the microparticles of claims 18 and 19.

Claim 18 is directed to a homogenous microparticle prepared according to claims 1-9. As mentioned in Section IV, above, Example 1 and the corresponding disclosure of Ratwatte is directed to a coated, non-homogenous particle. Example 2 and the corresponding disclosure of Ratwatte use a mixture ***without polymer*** to prepare microparticles. In contrast, the process of method claims 1-9, and the microparticles of claim 18, require the presence of polymer in an amount at least 5% by weight based upon the dry content of the liquid medium.

Thus, for all of the .foregoing reasons, Ratwatte fails to disclose the homogenous microparticle of claim 18. Furthermore, the Declaration and comparative data show that the microparticles of the claimed invention are better than the particles in Examples 6-8 which are similar to particles prepared by Ratwatte without polymer. (Declaration at ¶10)

Claim 19 relates to the microparticle of claim 18 further comprising a polymeric film coating. If Ratwatte fails to anticipate the microparticle itself, i.e., the microparticle of claim 18, then Ratwatte must also fail to anticipate the microparticle of claim 18 further comprising a polymeric film coating.

For all of the foregoing reasons, withdrawal of the §102 rejection is requested.

CONCLUSION

Upon entry of this Amendment, claims 1-23 remain pending. Applicant respectfully submits that claims 1-23 are directed to patentable subject matter. Accordingly, Applicant requests allowance of the claims.

Authorization is hereby given to charge any fee in connection with this communication to Deposit Account No. 23-1703.

Dated: 8 October 2003

Respectfully submitted,

John M. Genova
Reg. No. 32,224
Attorney for Applicant

Customer No. 07470
Direct Line: (212) 819-8832

Attachment: RCE Transmittal (PTO/SB/30)

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13/ Requested 1.114

PTO/SB/30 (09-03)
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	09/674,043
Filing Date	23 october 2000
First Named Inventor	Brita Sjoblom
Art Unit	1615
Examiner Name	A. Pulliam
Attorney Docket Number	1103326-0642

Bet 10-23-03

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☑ Amendment/Reply

      ii. ☑ Affidavit(s)/ Declaration(s)

      iii. ☐ Information Disclosure Statement (IDS)

      iv. ☐ Other _____

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 23-1703

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☐ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☑ Other any other fees which may be due with this filing

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☐ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED			
Name (Print/Type)	John M. Genova	Registration No. (Attorney/Agent)	32,224
Signature	John M. Genova	Date	October 8, 2003

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Name (Print/Type)	John M. Genova		
Signature	John M. Genova	Date	October 8, 2003

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P. . Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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1103326-0642

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Brita Sjöblom
Serial No.	:	09/674,043
Filed	:	October 23, 2000
For	:	METHOD TO OBTAIN MICROPARTICLES
Examiner	:	A. Pulliam
Art Group	:	1615

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. 1.8

I hereby certify that this paper is being facsimile transmitted to the U.S. Patent and Trademark Office on 8 October 2003 at the facsimile number 703-305-3592.

John M. Genova — 32,224
Attorney Name — PTO Reg. No.

John M Genova — 8 Oct 2003
Signature — Date of Signature

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Mail Stop RCE
Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTENTION: **Examiner A. Pulliam**
FACSIMILE NO: **703-305-3592**
DATE: **8 October 2003**
PAGES: **3 pages** (including RCE Transmittal (PTO/SB/30)

LETTER

Sir:

On today's date, Applicant submitted a Request for Continued Examination ("RCE") Transmittal (PTO/SB/30) and an Amendment by facsimile transmission. Subsequent to that transmission, the undersigned Attorney noticed that the "Certificate of Mailing or Transmission" appearing on the RCE transmittal had been signed but that the RCE transmittal itself had not been signed.

Accordingly, the RCE transmittal is being re-transmitted with all of the required signatures.

Authorization is hereby given to charge any fee in connection with this communication to Deposit Account No. 23-1703.

Dated: 8 October 2003

Respectfully submitted,

John M. Genova
Reg. No. 32,224
Attorney for Applicant

Customer No. 07470
Direct Line: (212) 819-8832

Attachment: RCE Transmittal (PTO/SB/30)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

14/Declaration
1.132

Applicant	:	Brita Sjöblom
Serial No.	:	09/674,043
Filed	:	October 23, 2000
For	:	METHOD TO OBTAIN MICROPARTICLES
Examiner	:	A. Pulliam
Art Group	:	1615

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CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. 1.8

I hereby certify that this paper is being facsimile transmitted to the U.S. Patent and Trademark Office on 8 October 2003 at the facsimile number 703-305-3592.

John M. Genova — 32,224
Attorney Name — PTO Reg. No.

John M Genova — 8 Oct 6/ 2003
Signature — Date of Signature

Mail Stop RCE
Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTENTION: **Examiner A. Pulliam**
FACSIMILE NO: **703-305-3592**
DATE: **8 October 2003**
PAGES: **16 pages**

Declaration of Anne Mari Juppo
(Under 37 C.F.R. §1.132)

Sir:

I, Anne Mari Juppo, declare as follows:

1. I am a citizen of Finland. I graduated in 1995 from the University of Helsinki, Finland, with a doctorate in Pharmaceutical Technology.

2. The assignee of the referenced application is AstraZeneca AB. I am presently employed by AstraZeneca and my current position is Team Manager/Principal Scientist in Product Development. I have held this position since 2000. During the period 1996-2000, I was employed as a research scientist and project leader in Pharmaceutical Technology Solids and as a research scientist in Product Development.

In addition to my employment at AstraZeneca, I have been an adjunct professor since 2001 in Pharmaceutical Product Development at the University of Helsinki, Finland. My curriculum vitae is attached to this Declaration as Exhibit A.

3. I have read and understood the referenced patent application. I am familiar with the invention described and claimed therein.

4. The claimed invention is directed to a method for the preparation of homogeneous microparticles comprising a pharmaceutically active substance and a polymer. Specifically, a liquid medium having a minimum dry content of 15% by volume is atomized into droplets. The liquid medium comprises a pharmaceutically active substance, a polymer present in the amount of at least 5% by weight based upon the dry content of the liquid medium, and a liquid in which the pharmaceutically active substance and polymer are suspended, dissolved or emulsified. The droplets are frozen by a cold medium, e.g., a liquid gas. The frozen liquid of the frozen droplets are sublimated to obtain dry, homogenous microparticles.

5. The homogenous microparticles obtained with the claimed method are characterized by a small pore size, low friability, and a high content of the pharmaceutically active substance. Advantageously, microparticles prepared in accordance with the claimed method have a low friability and other mechanical properties enabling them to undergo a fluidized bed coating process without disintegrating or otherwise losing their shape and structural integrity.

6. It was unexpectedly discovered that the success in obtaining stronger microparticles, i.e., porous microparticles having low friability, depends on the volume fraction of dry materials and the amount of polymer binder. Therefore, in accordance with the claimed invention, the minimum dry content of the suspension/solution/emulsion from which the droplets are formed is 15% by volume and the polymer binder content is at least 5%.

7A. It is my understanding GB 2 329 124 to Ratwatte ("Ratwatte") has been cited against the patentability of the claimed invention.

7B. Example 1 of Ratwatte discloses a method wherein an agent composition is dispersed in a solution of a coating material in a liquid carrier material to form a dispersed mixture which is then sprayed to form droplets of the dispersed mixture. The droplets are frozen and dried to produce a plurality of coated individual particles.

7C. Example 2 of Ratwatte appears to disclose a method of preparing homogenous microparticles. However, the method and microparticles of Example 2 of Ratwatte are different from the claimed invention. In accordance with Example 2 of Ratwatte, a mixture is formed by

adding a drug to a stabilizing formulation consisting of water, a carbohydrate and a surfactant. In contrast to the claimed invention, polymer is absent from the mixture. The mixture without polymer is sprayed from a nozzle into a moving stream of air that is cooled below the freezing point of the mixture to form frozen droplets which are freeze-dried to produce particles consisting of a homogenous mixtures of the drug and stabilizing formulation. Ratwatte discloses that the particles of Example 2 can be coated in the same way as the particles of Example 1.

8A. A working example of the claimed invention is provided by Example 1. As shown in Example 2, the homogeneous particles of Example 1 are coated by a fluidized bed coating process without disintegrating or otherwise losing their shape and integrity.

8B. The following Examples 3-10 follow the preparation of microparticles in accordance with the procedure of Example 1. Only original Example 1 and Example 3 meet the requirements of the claimed invention wherein the minimum dry content of the suspension/solution/emulsion from which the droplets are formed is 15% by volume and the polymer binder content is at least 5%. In Examples 4-10, the minimum dry content and/or polymer binder content deviate from the express requirements of the claimed invention. The table provides a summary of the contents and properties of the respective particles prepared in accordance with Examples 1 and 3-10.

Example 3: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	300 g
HPMC, 6 cps	79.7 g
Tween 80 (polysorbate 80)	6 g
Purified water	827.4 g

Weight percent of dry content in suspension: 31.8 (17.7 vol%).

Preparation of slurry and particles was done as in the example 1. The bulk density, median pore size and mechanical strength was measured and the results are shown in Table 2.

Example 4: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	150 g
HPMC, 6 cps	39.9 g
Tween 80 (polysorbate 80)	3 g
Purified water	801.3 g

Weight percent of dry content in suspension: 19.4 (10 vol%).

Preparation of slurry and particles was done as in the example 1. The bulk density, median pore size and mechanical strength was measured and the results are shown in Table 2.

Example 5: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	150 g
HPMC, 6 cps	7.9 g
Purified water	449.4 g

Weight percent of dry content in suspension: 26 (12 vol%).

Preparation of slurry and particles was done as in the example 1. The bulk density, median pore size and mechanical strength was measured and the results are shown in Table 2.

Example 6: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	60 g
Purified water	201 g

Weight percent of dry content in suspension: 23 (9.8 vol%).

Preparation of slurry and particles was done as in the example 1. The particles prepared were too fragile for handling.

Example 7: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	60 g
Purified water	440 g

Weight percent of dry content in suspension: 12 (4.7 vol%).

Preparation of slurry and particles was done as in the example 1. The particles prepared were too fragile for handling.

Example 8: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	183.7 g

Tween 80 (polysorbate 80)	4 g
Purified water	300 g

Weight percent of dry content in suspension: 38.5 (19.1 vol%).

Preparation of slurry and particles was done as in the example 1 except that the pressure of the atomizer was 0.5 bar. The particles were fragile.

Example 9: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	100 g
HPMC, 6 cps	1.5 g
Tween 80 (polysorbate 80)	2 g
Purified water	155.3 g

Weight percent of dry content in suspension: 40 (20.3 vol%).

Preparation of slurry and particles was done as in the example 1 except that the pressure of the atomizer was 0.25 bar. The particles were fragile.

Example10: Preparation of microparticles

A suspension containing talc powder was made according to the composition below:

Talc powder (1-2 μm)	100 g
HPMC, 6 cps	3.0 g
Tween 80 (polysorbate 80)	2 g
Purified water	157.5 g

Weight percent of dry content in suspension: 40 (20.6 vol%).

Preparation of slurry and particles was done as in the example 1 except that the pressure of the atomizer was 0.25 bar. The particles were fragile.

Table
Characterization of microparticles

Example no	Dry content (wt%)	Dry content (vol %)	Binder (wt%)	Mercury porosity measurements		Mechanical strength	
				Bulk density	Pore median size (μm) (measured range: 0.0005-10μm)	kPa	Fraction
1	34	19.2	21	0.47	0.8	94	450-630 μm
3	31.8	17.7	21	0.48	0.7	125	300-400 μm
4	19.4	10	21	0.23	1.8	62	300-400 μm
5	26	12	5	0.35	1.6	25	300-400 μm
6	23	9.8	0	Not measured		Too fragile for handling	
7	12	4.7	0	Not measured		Too fragile for handling	
8	38.5	19.1	0	Not measured		Fragile, not coatable	
9	40	20.3	1.5	Not measured		Fragile, not coatable	
10	40	20.6	3	Not measured		Fragile, not coatable	

Of these examples, the particles from Examples 1 and 3 were tested and showed to endure the fluidisation in the fluid bed coating process.

9. As can be seen from the Table, the properties of the microparticles are a function of the relationship between the minimum dry content and the polymer binder content. The particles of Examples 1 and 3 possess the mechanical properties to be successfully coated by a fluidized bed coating process. The particles of Examples 4-10, wherein the minimum dry content is less than 15% by volume and/or the polymer binder content is less than 5%, are either too fragile for handling or do not possess the threshold mechanical properties to be coated by a fluidized bed coating process.

10. The comparative data shows that a better result is achieved with the claimed invention. Specifically, the microparticles prepared in accordance with Examples 1 and 3 have superior mechanical strength in comparison to the pellets of Examples 6-8 which, similar to Example 2 of Ratwatte, were prepared from a mixture without polymer, i.e., a binder.

Conclusion

Advantageously, the homogenous microparticles obtained with the claimed method are characterized by a small pore size, low friability, and a high content of the pharmaceutically active substance. It was unexpectedly discovered that the success in obtaining stronger microparticles, i.e., porous microparticles having low friability, depends on the volume fraction of dry materials and the amount of polymer binder. In accordance with the claimed invention, therefore, the minimum dry content of the suspension/solution/emulsion from which the droplets are formed is 15% by volume and the polymer binder content is at least 5%. The claimed microparticles having a low friability can withstand coating with a polymeric film.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated:

Anne Mari Juppo

CURRICULUM VITAE

1. FULL NAME

Anne Mari Juppo

2. DATE AND PLACE OF BIRTH

661122, Töysä, Finland

221166-172M (Finnish ID number)
661122-2925 (Swedish ID number)

3. EDUCATION

850531	Graduated from Alavus High School, Finland
910425	**M.Sc. degree** in pharmacy, University of Helsinki, Finland
951117	**Ph.D. degree** in pharmaceutical technology, University of Helsinki, Finland
971231	**Docent degree** (associate professor) in pharmaceutical technology, University of Helsinki, Finland
030101	**Adjunct professor** in pharmaceutical product development, University of Helsinki, Finland

4. PROFESSIONAL APPOINTMENTS

1985-1990	**Pharmacist** (part-time) in several retail pharmacies (total 10 months) in Finland
860617-860822	Employed at a **pharmaceutical whole-sale company** Oriola, Seinäjoki, Finland
890515-890815	Employed at a pharmaceutical company, Medipolar, Farmos Corp., in Oulu, Finland. **Product development projects of large-volume parenteral preparations, substitute for production department manager.**
900822-920405	**Assistant teacher** at the University of Helsinki, Department of Pharmacy, Pharmaceutical Technology Division, Helsinki, Finland
920406-951031 **951101-951219**	**Research Scientist** and **Senior Research Scientist** in the Laboratory of Physics, Department of Physical Pharmacy, Orion Pharma, Orion Corp., Espoo, Finland. Note that this was a full-time appointment in addition to parallel Ph.D. studies.
960102-990930	**Research Scientist/Project leader** at Astra Hässle AB, Pharmaceutical Technology Solids, Mölndal, Sweden.
991001-001130	**Research Scientist** at AstraZeneca R&D Mölndal, Product Development, Formulation II, Mölndal, Sweden.
Since 001201	**Team Manager/Principal Scientist** at AstraZeneca R&D Mölndal, Product Development, Mölndal, Sweden

5. KNOWLEDGE OF LANGUAGES

Finnish	Mother tongue
English	Understood: excellent
	Written: go d
	Spoken: good
Swedish	Understood: excellent
	Written: good
	Spoken: excellent
German	Understood, written and spoken: poor

6. OTHER ACADEMIC AND PROFESSIONAL ACTIVITIES

Secretary of the Organising Committee of Pharmaceutical Technology and Biopharmacy Section of XI Helsinki University Course in Drug Research, Espoo, 6-7 June, 1991

Board member (1994) and secretary (1995) of the Finnish Pharmacists' Society

Member of the committee of the post-graduate specialized studies in Industrial Pharmacy at the University of Helsinki, 1995 (representing the Finnish Pharmacists' Society)

7. RESEARH AWARDS, RESEARCH HONOURS AND MAJOR STIPENDIARY SUPPORT FOR RESEARCH

Award from the M.Sc. thesis with honors, Department of Science, Faculty of Philosophy, May 1991, 1500 FIM

Lars Grenman award from the most successful M.Sc. studies in practical pharmacy, Department of Science, Faculty of Philosophy, May 1991, 400 FIM.

Award from the M.Sc. studies, The society of pharmacy students at the University of Helsinki, January 1992, 1000 FIM

Scholarship for a young scientist for Ph.D. studies, the Foundation of the 350th Anniversary of University of Helsinki, March 1992, 70 000 FIM

Award from the best thesis of the year in particle technology, the Finnish Particle Society, October 1995, 5000 FIM

8. EDITORIAL BOARD MEMBERSHIP

Editor of the Journal of Society of Physical Pharmacy, 1992-1994

Editor of the Proceedings of the 5th Symposium of Physical Pharmacy, Society of Physical Pharmacy, Espoo, January 1994

9. REFEREE OF SCIENTIFIC JOURNALS AND RESEARCH PROJECT GRANT APPLICATIONS

European Journal of Pharmaceutical Sciences 1999-

The Netherlands Organization for Scientific Research (NWO) 1999

Katholieke Universiteit Leuven 2003

Powder Technology 2003-

10. MEMBERSHIP IN SCIENTIFIC SOCIETIES

Society of Physical Pharmacy, since 1990, editor of the journal, 1992-1994

The Finnish Pharmaceutical Society, 1990-1991

The Finnish Particle Society, 1992-1995, deputy board member 1995

American Association of Pharmaceutical Scientists, since 1996

Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik, since 1999

European Federation of Chemical Engineering (EFCE), Working Party on Agglomeration, representant for Sweden, since 2001

11. SCIENTIFIC COURSES AND CONFERENCES

Granulation and pelletization (Marc Donsmarck), Helsinki, Finland	890925
1st Symposium of the Society of Physical Pharmacy, Turku, Finland	900130
Minisymposium. Granulation - End Point Control - Process Automation, Espoo, Finland	900410
Education seminar in Pharmaceutical Technology: Development of drug formulation and manufacturing process, Tvärminne, Finland	901119-20
2nd Symposium of the Society of Physical Pharmacy, Espoo, Finland	910130
10th Pharmaceutical Technology Conference, Bologna, Italy	910416-18
XI Helsinki University Course in Drug Research, Espoo, Finland	910606-07
APV 38. Jahreskongress, Aktuelle Hilfstoffe für die Arzneimitteltechnologie, Regensburg, Germany	920401-04
Biomaterials in Surface and Colloid Science, The 2nd National Symposium of Surface and Colloid Science, Espoo, Finland	920827-28
4th Symposium of the Society of Physical Pharmacy, Turku, Finland	930122
Seminar in Granulation and Pelletisation, University of Helsinki, Lammi, Finland	930315-16
Characterisation of Porous Solids, COPS IUPAC Congress, Marseille, France	930509-12
XII Helsinki University Course in Drug Research, Espoo, Finland	930617-18
5th Symposium of the Society of Physical Pharmacy, Espoo, Finland	940127
Course: Powder Flow properties , Stockholm, Sweden	940926
Particle seminar, Finn Metric, Espoo, Finland	941107
Accelerating drug discovery and development, AAPS 10th Annual Meeting & Exposition, Miami Beach, USA	951105-09
Advances in the Pharmaceutical Sciences: Contributing to Society, AAPS Annual Meeting & Exposition, Seattle, USA	961027-31
Läkemedelskongressen, Älvsjö, Sweden	961111-13
Course: Supercritical Fluid Technology in Drug Delivery Research, Zürich, Switzerland	970410-11
Annual meeting of the International Fine Particle Research Institute, Brighton, UK	980629-0703
World Congress on Particle Technology, Brighton, UK	980706-09
AAPS Annual Meeting, New Orleans, USA	991115-18
Annual meeting of the International Fine Particle Research Institute, Den Haag, The Netherlands	000709-11
Solid oral dosage forms, Malmö, Sweden	010513-15
World Congress in Particle Technology, Sydney, Australia	020722-25

12. SCIENTIFIC PUBLICATIONS

1. A.M. Juppo, J. Yliruusi and L. Kervinen, 1991. The effect of compression pressure and compression speed on disintegration time and tensile strength of lactose, glucose and mannitol tablets. Proceedings of 10th Pharmaceutical Technology Conference, Bologna, Italy, April 16th-18th 1991, Vol 1, 558-567.

2. A.M. Juppo, J. Yliruusi, L. Kervinen and P. Ström, 1992. Determination of size distribution of lactose, glucose and mannitol granules by sieve analysis and laser diffractometry. Int. J. Pharm. 88, 141-149.

3. J.P. Mannermaa, E. Muttonen, J. Yliruusi and A. Juppo, 1992. Comparison of different rubber stoppers; The effect of sterilization on the number of particles released. J. Parenteral Sci. Technol. 46, 73-77.

4. A.M. Juppo, J. Yliruusi and L. Kervinen, 1993. The effect of compression pressure and compression speed on disintegration time and tensile strength of lactose, glucose and mannitol tablets. Pharmaceutical Technology, Tableting Technology, Compression, Vol. 2, Eds. M.H. Rubinstein. J.I. Wells, Ellis Horwood, 129-134.

5. L. Juslin, A.M. Juppo and J. Yliruusi, 1993. Effect of different relative humidities on the water vapour sorption to theophylline anhydrate and two different alprazolam hydrochloride crystal modifications. Boll. Chim. Farm. 133, 395-400.

6. A.M. Juppo and J. Yliruusi, 1994. Effect of amount of granulation liquid on total pore volume and pore size distribution of lactose, glucose and mannitol granules. Eur. J. Pharm. Biopharm. 40, 299-309.

7. A.M. Juppo, L. Kervinen, J. Yliruusi and E. Kristoffersson, 1995. Compression of lactose, glucose and mannitol granules. J. Pharm. Pharmacol. 47, 543-549.

8. A.M. Juppo, L. Kervinen and J. Yliruusi, 1995. Skewness and kurtosis values of force-time profiles obtained from compression of lactose, glucose and mannitol granules. Eur. J. Pharm. Biopharm. 41 (6) 374-381.

9. A.M. Juppo, 1995. Pore structure of lactose, glucose and mannitol tablets compressed from granules and dependence of breaking force of tablets on porosity parameters studied by mercury porosimetry. Dissertation thesis, University of Helsinki, p. 38.

10. A.M. Juppo, 1996. Relationship between breaking force and pore structure of lactose, glucose and mannitol tablets. Int. J. Pharm. 127, 95-102.

11. A M Juppo, 1996. Porosity parameters of lactose, glucose and mannitol tablets obtained by mercury porosimetry. Int. J. Pharm. 129, 1-12.

12. A.M. Juppo, 1996. Change in porosity parameters of lactose, glucose and mannitol granules caused by low compression force. Int. J. Pharm. 130, 149-157.

13. S. Westermarck, A.M. Juppo, K. Koiranen and J. Yliruusi, 1998. Mercury porosimetry of pharmaceutical powders and granules. J. Porous Materials 5, 77-86.

14. A.M. Juppo, L. Hellén, V. Pullinen, K. Kalsta, J. Yliruusi and E. Kristoffersson, 1997. Application of mercury porosimetry in evaluation of the extrusion-spheronisation process. Eur. J. Pharm. Biopharm. 44, 205-214.

15. S. Westermarck, A.M. Juppo, L. Kervinen and J. Yliruusi, 1998. Pore structure and surface area of mannitol powder, granules and tablets determined with mercury porosimetry and nitrogen adsorption. Eur. J. Pharm. Biopharm. 46, 61-68.

16. M.-L. Andersson, C. Boissier, A.M. Juppo and A. Larsson, 1998. **Patent**: Incorporation of active substances in carrier matrixes. WO99/52507.

17. C. Boissier and A.M. Juppo, 1998. **Patent application**: A method of producing drug particles. WO 00/30612.

18. S. Westermarck, A.M. Juppo and J. Yliruusi, 1999. Microcrystalline cellulose and its microstructure in pharmaceutical processing. Eur. J. Pharm. Biopharm. 48, 199-206.

19. P. Luukkonen, T. Schæf r, L. Hellen, A.M. Juppo and J. Yliruusi, 1999. Rheological characterization of silicified microcrystalline cellulose wet masses using a mixer torque rheometer. Int. J. Pharm. 188, 181-192.

20. S. Westermarck, A.M. Juppo and J. Yliruusi, 2000. Mercury porosimetry of mannitol tablets. Pharm. Dev. Technol. 5, 181-188.

21. A.M. Juppo, 2002. **Patent application:** Novel modified release formulation. WO02/064118.

22. A.M. Juppo, 2002. **Patent application:** Novel modified release formulation WO02/064121.

23. M. Savolainen, C. Khoo, H. Glad, C. Dahlqvist and A.M. Juppo, 2002. Evaluation of controlled release polar lipid microparticles. Int. J. Pharm. 244, 151-161.

24. A.M. Juppo, C. Boissier and C. Khoo, 2003. Evaluation of solid dispersion particles prepared with SEDS. Int. J. Pharm. 250, 385-401.

25. N. Laitinen and A.M. Juppo, 2003. Measurement of pharmaceutical particles using a time-of-flight particle sizer. Eur. J. Pharm. Biopharm. 55, 93-98.

26. M Savolainen, C. Khoo, K. Lövqvist, H. Glad, C. Dahlqvist, A.M. Juppo., 2003. Evaluation of controlled release polar lipid-hydrophilic polymer microparticles. Int. J. Pharm. 262, 47-62.

27. A. Jørgensen, P. Luukkonen, J. Rantanen, T. Schæfer, A.M. Juppo and J. Yliruusi., 2003. Comparison of torque measurements and NIR spectroscopy in characterisation of wet granulation. To be submitted.

13. PEDAGOGIC MERITS

Practical teaching

Assistant teacher, University of Helsinki, August 1990 - April 1992:
Work included demonstrations and teaching and supervision of the laborative work as well as checking work reports and being an examinator for two courses for pre-graduate pharmacy students per year: Drug preparations and excipients and Product development. As an assistant teacher, this practical teaching work took approximately 70% of the working time.

Mathematical exercises in pharmaceutical statistics, University of Helsinki, February 1991 and February 1993:
Planning and supervision of the exercises on statistics course, where the descriptive statistics were used in the pharmaceutical technology cases.

Responsibility of the training of the laboratory staff, Laboratory of Physics, Department of Physical Pharmacy, Orion-Farmos, Finland April 1992 - August 1994:
Planning and organisation of both the internal training and the training given by the laboratory to the other units of the company.

Lectures as an associate professor in Helsinki University:
Microparticulate systems course (16 hours, including lectures and tutorial teaching), 1998, 2000.
How does novel drug discovery technologies affect pharmaceutical product development in future? In lecture serie: Medicine in future (2 hours, lectures), 2001, 2002, 2003.

Choice of composition – decision process (2 hours, lectures) 2003, Specialist studies in Industrial Pharmacy, Formulation I

Tutorial work

Tutor for five M.Sc. thesis works in University of Helsinki:
S. Björklund, 1993. Effect of moisture on the flowability of lactose, mannitol and microcrystalline cellulose powders
S. Westermarck, 1993. Effect of moisture and scanning speed on the analysis result obtained from mercury porosimetry of granules and tablets,
N. Laitinen, 1997. Characterisation of pharmaceutical particles.
V. Pullinen-Strander, 1999. Application of mercury porosimetry in evaluation of the extrusion-spheronisation process.
M. Savolainen, 2001. Preparation of controlled-release felodipine microparticles.

Tutor for a Ph.D. work in University of Helsinki:
S. Westermarck, 1993-2000. Effect of moisture and scanning speed on the mercury porosimeter analysis of mannitol and microcrystalline cellulose granules and tablets.

Mentorship

Mentor at Chalmers University of Technology for Ph.D. student Catherine Boissier, since 1999.

Examination board membership
Barbro Johansson: Tabletting behaviour of aggregates, Uppsala University, 1999.
Helena Ohlsson: Particle interactions and internal tablet structure, Uppsala University, 2000.
Sofia Mattson: Pharmaceutical binders and their function in directly compressed tablets, Uppsala University, 2000.
Susanne Bredenberg: New concepts in administration of drugs in tablet form, 2003.

Referee to Ph.D. thesis
Merja Riippi: Physicochemical properties of erythr mycin acistrate tablets, University of Helsinki, 2001
Pirjo Luukkonen: Rheological properties and the state of water of microcrystalline cellulose and silicified microcrystalline cellulose wet masses, University of Helsinki, 2001.

Refere to Docent (Associate professor) degree

Jukka Rantanen, Docent in physical pharmacy, University of Helsinki, 2001.

Development of pharmaceutical education

Member of the committee of the post-graduate studies for specialisation in Industrial Pharmacy at the University of Helsinki, Department of Pharmacy, 1995:
The task for this committee was to plan the curriculum and courses for specialised studies in Industrial Pharmacy (representing the Finnish Pharmacists' Society). These studies are equivalent to the licentiate examination in pharmacy.

University of Helsinki, studies for specialisation in Industrial Pharmacy and Pharmaceutical Technology, Planning of a course in Formulation, 8 credits, 2003.

Teaching material

University of Helsinki, Department of Pharmacy, Pharmaceutical Technology Division, August 1990 -April 1992:
Revision of the teaching material for two laboratory courses: Drug preparations and excipients and Product development.

University of Helsinki, Department of Pharmacy, Pharmaceutical Technology Division, 1998:
Teaching material for the course: Microparticulate systems.

Popular science

Lectures on a course for the staff working in the social care of elderly people: Medicines and their use, Alavus-Töysä open college, October 1991:
This course was organised as a part of popularisation of science at the University of Helsinki.

14. ADMINISTRATIVE MERITS

Substitute for production department manager at a pharmaceutical company, Medipolar, Farmos Corp., in Oulu, Finland in May-August 1989. This included the responsibility of the production of large-volume parenterals and parenteral nutrition solutions and a shared responsibility of batch protocols and the release of production batches. Skills in operation of a production department were obtained.

Research Scientist (April 1992 - October 1995) and **Senior Research Scientist** (November 1995 - December 1995) in the Laboratory of Physics, Department of Physical Pharmacy, Orion-Farmos, Orion Corp., Espoo. I supervised the work of laboratory technicians. My role was to be an interpreter between Laboratory of Physics and other departments when solving problems in product development, purchasing of raw materials, production of active substance and production of pharmaceuticals. Thus, skills in working with people with different backgrounds were obtained. Laboratory of Physics had a staff of physicists, chemists, engineers and pharmacists.

Project leader at Astra Hässle AB, Pharmaceutical Technology Solids, in Mölndal, Sweden, 1996-1999. The appointment included planning and leading of a 3-year exploratory research project which concerned the entire Pharmaceutical R&D at Astra Hässle AB, and even other companies in Astra Corporation. The project leadership included supervision and leading of scientific work of 15 persons (8 man-years) in project organisation. Knowledge in project start-up, project planning, setting goals and milestones, achieving them, group dynamics, leadership in matrix organisation and in patent work was obtained.

Team Manager at AstraZeneca R&D Mölndal, Product Development, Formulation II, Sweden, since 2000. Leading a group of 8 scientists with different backgrounds including polymer chemists, polymer physicists, surface and colloid chemists, pharmacists, and chemical engineers.

Administrative courses:

980810-12	Practical project leadership II, IIR Utbildning AB, Stockholm, Sweden.
011022-24	Leadership and team development, AstraZeneca, Sweden
2002-2003	Development group in leadership, AstraZeneca, Sweden